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Malaria has long been a major cause of mortality within the Armed Forces (AF), historically inflicting heavier casualties than combat injuries [1]. Advances have been made in preventing malaria transmission; nonetheless, military personnel deploying to areas with malaria continue to be vulnerable to the disease.

Antimalarial drug resistance is a leading challenge in the control of malaria. Chloroquine resistant strains of malaria, such as *Plasmodium falciparum*, are responsible for most human malaria cases and can be found across several regions of Southeast Asia, South America, and Africa [2]. There are currently three licensed anti-malarial drugs against chloroquine resistant *Plasmodium falciparum* malaria: mefloquine (trade name: Lariam[®]), doxycycline, and a combination of atovaquone and proguanil (trade name: Malarone[®]). These agents differ in their active ingredients, side effects, dosages, cost and contraindications, and as with any drug, need to be prescribed appropriately given an individual's medical history. For example, to minimise risk of adverse reactions mefloquine must not be prescribed for patients with active or history of psychiatric disorders [3]. However, it is important to recognise that there is no single anti-malarial that is 100% effective against all the different strains of malaria and all three antimalarials can cause adverse effects [4].

Mefloquine has received considerable media attention following incidents involving US soldiers committing acts of violence while taking the drug [5]. Formal inquests have since refuted that mefloquine was the cause, with there being no evidence to support a causal link between taking the drug and the violent responses [6]. Nonetheless, as a result of the media interest, the use of mefloquine within military settings is now somewhat controversial [7].

Use of mefloquine in the AF

Many international AF currently include mefloquine in their chemoprophylactic treatments, not specified as agents of last resort, including the Irish and Canadian AF. Presently, the UK Ministry of Defence (MoD) supports the prescription of mefloquine to AF personnel where it is deemed to be the appropriate medication [6]. Counter to this stance, the US military and Australian Defence Forces (ADF)[8] restrict mefloquine's use to a third-line drug, only prescribed when there are contraindications to other antimalarials. The drug is banned altogether by certain US military units (e.g. Special Forces, aviators and divers) [9].

Responses to mefloquine in military personnel

Some evidence of potential adverse mefloquine effects stems from a study which examined Swedish soldiers prescribed mefloquine or another antimalarial [10]. Adverse effects, including neuropsychological effects, were more commonly reported in the mefloquine group (see Table 1). Similarly, in a study of 4,123 Italian AF regulars, 21.2% (n= 875) of those prescribed mefloquine reported adverse events. However, no serious adverse events were reported, and authors concluded 'good tolerability of mefloquine in the military' [11]. In US troops, deployed personnel prescribed mefloquine were significantly more likely to experience anxiety, while non-deployed personnel prescribed mefloquine were significantly more likely to experience symptoms of posttraumatic stress disorder (PTSD) [12]. This difference in non-deployed personnel may potentially reflect a healthy warrior effect [13].

Nevertheless, several studies have reported few or no adverse responses to mefloquine in other military samples. In the British AF, research found that of 486 personnel prescribed mefloquine only 11 individuals reported adverse side effects [6]. Furthermore, a study of UK personnel in East Africa [14] found mefloquine was no more problematic with respect to side effects than the chloroquine/proguanil regime.

However, the small numbers of participants in these studies may limit the generalisability of the findings. In the ADF, of 1,157 participants, only 6.5% (n=75) of personnel taking mefloquine withdrew from the trial because of adverse responses to the drug and the rate of adverse side effect reporting was similar across antimalarials [15]. Finally, Defence Statistics found that between 2009-2010, UK AF personnel prescribed mefloquine or a different antimalarial were equally likely to be assessed as having a mental health disorder. However, Defence Statistics did not have data available to allow them to determine whether the reason for assessment was due to the prescription of an antimalarial drug or other potentially confounding factors. For example, this time period corresponds with the highest number of casualties the UK AF sustained in Afghanistan [16].

Factors which may influence the experience of mefloquine side effects

First, the military environment can expose individuals to challenging conditions that may cause some symptoms similar to the side effects of mefloquine. For instance, the stress of deployment, sleep deprivation and high intensity operations could lead to increased anxiety and sleep disturbances which are known side effects of the drug. Secondly, it is possible that mental health-related stigma or fears of falling short of the medical criteria that deems personnel fit to deploy [17] may contribute to under-reporting of mefloquine side effects. This reluctance to present prevents individuals being switched to an alternative medication and inhibits the medical community's understanding of the true impact of the drug within this population. Lastly, there is evidence in civilian populations of increased risk of psychiatric illness in female mefloquine users [18] and little research has been done to identify if this might place female service personnel at increased risk.

Directions for future research

There is no clear evidence that mefloquine use by military personnel presents a disproportionate risk to their mental health. Nonetheless, several shortfalls in the current literature exist, including a lack of detail on exactly which side effects are being described, highlighting a need for future studies with a more transparent methodology. There are many distinct differences between military and civilian personnel (e.g. underlying fitness, greater exposure to hostile environments; sleep deprivation; stress) and further investigation of how these factors may contribute towards tolerance of antimalarials seems warranted.

Currently, mefloquine remains one of the World Health Organisation's essential drugs [19], and no national licensing authority has withdrawn mefloquine based on toxicity [3]. However, it is clear that the prescription of mefloquine to patients with a significant psychiatric history is contraindicated. Negative media attention and anecdotal evidence may also have contributed towards concerns regarding the harmful effects of mefloquine on mental health, especially in military personnel. Such misinformation may in itself heighten awareness of subjective symptoms, leading to increased reporting of side effects. There is evidence from military studies of vaccine administration that military personnel who perceived that they might experience side effects were more likely to do so [20]. We suggest that whilst more research is warranted, sensible and evidence-based reporting of the risks of mefloquine and risks of malaria should be readily available to ensure that troops who are prescribed the medication are not unduly worried whilst the medical staff who prescribe it remain alert to its potential to cause side effects.

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Table 1

Included studies sample characteristics, antimalarials administered and outcomes

Study	Military	Deployment location	N	Anti-malarial administered	Outcome
Andersson et al., 2008	Sweden	Liberia	1,170	Mefloquine, atovaquone/proguanil	Adverse events reported in 57% of the mefloquine group vs 34% in the atovaquone/proguanil group.
Eick-Cost et al., 2017	United States	Afghanistan, Iraq, Africa or other	367,840	Mefloquine, doxycycline, atovaquone/proguanil	Deployed mefloquine group more likely to experience anxiety compared with doxycycline recipients (IRR= 1.12, 95% CI 1.01-1.24). Non-deployed mefloquine group more likely to experience PTSD compared to atovaquone/proguanil recipients (IRR= 1.83, 95% CI 1.07-3.14)
Peragallo et al., 2014	Italy	Afghanistan	4,123	Mefloquine	Adverse events reported by 21.2% of personnel. No serious adverse events reported.
Ministry of Defence, 2017	United Kingdom	Afghanistan	486	Mefloquine	2.46% of personnel experienced adverse reactions. 1.8% of personnel required mefloquine to be withdrawn.
Croft et al., 1997	United Kingdom	East Africa	624	Mefloquine, chloroquine-proguanil	Incidence of adverse events was not significantly different between mefloquine and chloroquine-proguanil groups (OR 0.96; 95% CI 0.63-1.47). No serious adverse events reported.
Kitchener et al., 2005	Australia	East Timor	1,157	Mefloquine, doxycycline	57% of personnel prescribed mefloquine reported one or more adverse events vs 56% of doxycycline group.
Defence Statistics, 2016	United Kingdom	Kenya, Congo, Guinea, Ghana, Sierra Leone	116,704	Mefloquine, other antimalarial drug	10.0% of mefloquine group and 9.8% of other antimalarial drugs group assessed as having a mental health disorder in 2009-2010.

Note. IRR= incidence rate ratio. N= total number of participants. CI = confidence interval. PTSD = posttraumatic stress disorder. OR= odds ratio.